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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/814,338	03/21/2001	Jonathan M. Rothberg	21465-501 CIP2	6233
35437	7590	11/06/2003	EXAMINER	
MINTZ LEVIN COHN FERRIS GLOVSKY & POPEO			KIM, YOUNG J	
666 THIRD AVENUE			ART UNIT	
NEW YORK, NY 10017			PAPER NUMBER	

1637

DATE MAILED: 11/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/814,338	ROTHBERG ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-61,64-68,84-93 and 96-99 is/are pending in the application.
- 4a) Of the above claim(s) 1-55 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 56-61,64-68,84-93 and 96-99 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____. | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 5, 2003 has been entered.

Priority

As the claimed subject matter is found to lack support under 112, first paragraph, the effective priority date for this application is the instant filing date of March 21, 2001.

Election/Restrictions

Applicants are reminded that the instant application contains claims 1-55, drawn to inventions non-elected with traverse.

Applicants are requested to cancel the non-elected claims.

Information Disclosure Statement

Applicants appear to indicate that IDS submitted on February 1, 2002 have not been considered. Applicants are advised that Office Action mailed on November 19, 2002 (Paper No. 7), included the signed copy of its PTO-1449. A duplicate copy of the signed PTO-1449, as well

as Office Action Summary Sheet mailed on November 19, 2002, are attached to the instant Office Action for Applicants' record.

The Office acknowledges the receipt of the IDS submitted on June 12, 2003 and September 5, 2003 and the signed copy of the PTO-1449 forms are attached hereto.

Specification

The specification is objected to by the Examiner because it makes reference to an URL on the internet. For example, lines 20-21 of page 43 contains web-address. While information on web-address is accessible, the embedded hyperlinks and/or other forms of browser-executable code are impermissible and require deletion. The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference.

If the subject matter which is improperly incorporated by reference is directed to nonessential material (illustrating the state of the art), the deletion will probably not be considered as new matter. However, if the subject matter which is improperly incorporated by reference is directed to essential material, applicant will be required to amend the specification to include the subject matter incorporated. The amendment must be accompanied by an affidavit or declaration executed by the applicant stating that the amendatory material consists of the same material incorporated by reference.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56-61, 64-68, 84-93, and 96-99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claim 56 which serves as a base claim for dependent claims 57-61, 64-68, and 88-93; and claim 84 which serves as a base claim for dependent claims 84-87 and 96-99 have been amended to recite the limitation that the substrate of claim 56 (or an apparatus comprising the substrate) comprise a cavitated fiber optic wafer, wherein the wafer comprises a plurality of wells on top surface of the cavitated wafer and that the wells have, disposed thereon, *heads having a pyrophosphate sequencing reagent*.

This limitation is not supported by the specification, thereby lacking in the written description of the claims.

In the Amendment received on May 19, 2003, applicants have amended the invention as claimed to make the claims drawn to a substrate (and apparatus comprising the substrate), wherein the substrate comprises a cavitated fiber optic wafer, wherein the wafer comprises a plurality of beads each with a pyrophosphate sequencing reagent attached thereto (See page 5). Applicants, in support of this new limitation recited that proper support for the language could be found on page 31, lines 21-29.

On page 31, lines 21-29, the specification recites the following paragraph:

“In various embodiments, some components of the reaction are immobilized, *while other components are provided in solution*. For example, in some embodiments, the enzymes utilized in the pyrophosphate sequencing reaction (*e.g.*, sulfurylase, luciferase) may be *immobilized at the termini of a fiber optic reactor array*. Other components of the reaction, *e.g.*, a polymerase (such as Klenow fragment), nucleic acid template, and nucleotides can be added by flowing, spraying, or rolling. In still further embodiments, one or more of the reagents used in the sequencing reaction is *delivered on beads*.”

Although the paragraph mentions that the one or more reagents associated with beads, it is critical to understand the phrase in context. The paragraph is clear in stating that the components of the reaction are immobilized while the others are provided in solution (*i.e.*, not immobilized). It is clear that the sequencing reagents which were on beads are not immobilized by the language chosen, “reagents...[are]...*delivered* on beads.”

Additionally, nowhere in the specification substantiates this limitation, including the Examples given in the specification. For example, on page 53 at lines 31-32 (and Figure 1A to which Applicants refer in their remarks received on September 5, 2003, page 7), the specification discloses that the, “sulfurylase, apyrase, and luciferase are attached to the cavitated substrate using *biotin-avidin*.” It is known in the art that biotin-avidin binding is not considered to be beads.

Similarly claims 57, 67, 68, 84-87, and 96-99 recites that the nucleic acids are also disposed on the beads, wherein the beads are in the wells of the cavitated fiber optic wafer. This limitation is also nowhere to be found. The specification only recites that the nucleic acids are

immobilized on the wells of the cavitated fiber optic wafer, via biotin-avidin binding (page 6, lines 13-15), or generically describes that a solid substrate array “contains” a plurality of anchor primers covalently linked to a nucleic acid (page 8, lines 1-2; pages 10-11).

Even when the applicants contemplate the attachment of multiple nucleic acids on the solid support, attachment of the nucleic acids on the beads are not contemplated:

“Each sensitized site on a solid support is potentially capable of attaching multiple anchor primers (*or nucleic acids*). Thus, each anchor pad may include one or more anchor primers. It is preferable to *maximize the number of pads* that have only a single product reaction center (*e.g.*, the number of primer). This can be accomplished by techniques which include, but are not limited to: (i) varying the dilution of biotinylated anchor primers that are washed over the surface; (ii) varying the incubation time that the biotinylated anchor primers are in contact with the avidin surface; (iii) varying the concentration of open- or closed-circular template so that, on average, only one primer on each pad is extended to generate the sequencing template...” (page 13, lines 17-29; emphasis added).

Therefore, the claims as amended lack proper support, rendering the present New Matter rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 84-87 and 96-99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 84 recites the limitation "the nucleic acid disposed on beads." There is insufficient antecedent basis for this limitation in the claim. Claim 84 initially recites that the nucleic acid is disposed in the wells of the wafer, then refers to the nucleic acids disposed on beads, rendering the claims confusing as to whether the nucleic acids on the beads are the same as the nucleic acids disposed in the wells of the wafer. Claims 85-87 and 96-99 depend on the rejected claims, rendering said claims lacking in proper antecedent basis.

Claims 92, 93, and 98 recite the limitation "said sequencing reagent." There is insufficient antecedent basis for this limitation in the claim. Although the base claims of claims 92, 93, and 98 recite the term, "pyrophosphate sequencing reagent," the present rejection was necessitated by Applicants' amendment to claim 99 which specifically refers to the sequencing reagent as, "said pyrophosphate sequencing reagent." This renders claims 92, 93, and 98 indefinite in determining whether the "sequencing reagents" are or are not the same as the "pyrophosphate sequencing reagent."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 56-61, 64-68, 84-93, and 96-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chee et al. (2003/0108867 A1, issued June 12, 2003, priority April 20, 1999).

Claims 56-61, 64-68, 84-93, and 96-99 are drawn to a substrate and an apparatus comprising the substrate comprising a cavitated fiber optic wafer, wherein the cavitated fiber optic wafer is produced from a fused bundle of a plurality of individual optical fibers having a diameter between 3 and 100 μm , the cavitated fiber optic wafer comprising a depth of 0.5 mm to 5.0 mm; and wherein the cavitated fiber optic wafer comprises microspheres immobilized with nucleic acid and pyrosequencing reagents. Some embodiments are drawn to the various distances between the immobilized nucleic acids.

Chee et al. disclose a substrate (and apparatus comprising the substrate) for pyrosequencing a nucleic acid template, wherein the substrate is comprised of a bundle of plurality of fused, optical fibers which are “etched” such that small wells or depressions are formed at the end of the fibers (or cavitated) (Figure 1A-D, [0109], and [0112]). The cavitated optical fibers also comprise microspheres immobilized with capture probes ([0052]; claim limitation 57) and immobilized pyrosequencing reagents ([0057]).

Chee et al. disclose that the nucleic acids or DNAs ([0093]; claim limitation 87) are immobilized to the microspheres by linkers or covalently ([0015] and [0087]; claim limitation 67 and 68).

The substrate of Chee et al. is disclosed being able to have a wide range of nucleic acids, ranging from 10^2 to 10^9 ([0104]; claim limitation 64-66) as well as being chemically functionalized for photolithography ([0111]-[0114]; claim limitation 90, 91, 96, and 97).

The immobilized pyrosequencing reagents (on the microspheres, [0057]) are disclosed as being luciferase, sulfurylase, or apyrase ([0040]; claim limitation 92, 93, 98, and 99).

Although Chee et al. do not explicitly disclose that the imaging of the sequencing reaction is done through CCD (charge coupled device), such is implicit by the disclosure of the specification, wherein the artisans image the incorporated nucleotide in their fiber optic substrate ([0192]; claim limitation 86).

Chee et al. do not *explicitly disclose* the diameter of the individual optical fiber (claim limitation 58 and 85) nor the cavitated fiber optic wafer having a depth between 0.5 mm and 5.0 mm.

Chee et al. do not *explicitly disclose* various separation distance between the nucleic acids that are immobilized on the substrate or microspheres (claims 59-61).

Chee et al. do not explicitly disclose that a polished end of a fiber optic wafer is optically linked to a second fiber optic fiber (claims 88 and 89).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Chee et al. to arrive at the invention as claimed.

One of ordinary skill in the art, at the time the invention was made, would have been motivated to modify the teachings for the following reasons.

Although Chee et al. do not *explicitly disclose* various separation distance between the nucleic acids that are immobilized on the substrate or microspheres, which is drawn to the density of the array, such modification is considered to be well within the purview of an ordinarily skilled artisan.

This is evident in the disclosure by Chee et al., wherein the artisans state:

“In addition, one advantage of the present composition is that particularly through the use of fiber optic technology, extremely high *density* arrays can be made. Thus for example, because beads of 200µm or less (with beads of 200 nm possible) can be used, and very *small fibers are known*, it is possible to have as many as 40,000 or more (in some

instances, 1 million) different elements (e.g., fibers and beads) in a 1mm² fiber optic bundle, with densities of greater than 25,000,000 individual beads and fibers....” ([0105]).

Therefore, as evidenced above, it is determined that the modification of the separation distances between the nucleic acids as well as the modification of the diameters of the fiber optic strands, are well within the purview of an artisan’s desire on what density said artisan desires to achieve, allowing the artisan to have a reasonable expectation of success arriving at the invention as claimed.

Additionally, although the claims recite that the substrate now comprises a cavitated fiber optic *wafer*, the wafer is defined by the claim as a bundle of fiber optic strands having a front end and a distal end with the length of the bundle being 0.5 to 5.0 mm (Applicants’ term this “depth”). This limitation is obvious in view of making obvious aesthetic design changes. MPEP 2144.04 states that:

“The court found matters relating to ornamentation only ***which have no mechanical function cannot*** be relied upon to patentably distinguish the claimed invention from the prior art.” (*In re Seid*, 161 F.2d 229, 73 USPQ 431 (CCPA 1947)).

The instant situation is analogous to that which was described in the above case because the length of the fiber optic bundle does not materially affect the ability of the substrate to assay for ligand binding assays. This is further evident in Applicants’ claim 89 which requires that the ends of the shortened fiber optic bundles (of the wafer) be attached to second optical fiber bundles to be able to transmit the data across to the imaging device. The net effect, therefore, requires a long bundle of fiber optic fibers attached to an imaging device, all of which is disclosed by Chee et al. Since the distance between the cavitated end and the distal end of the

fiber optic fiber (i.e., depth) does not have any mechanical function, such limitation would not, “distinguish the claimed invention from the prior art.” (*In re Seid*), rendering the invention as claimed obvious over Chee et al. reference. Even if *arguendo* that the shortened length of the fiber optic bundle allows portability of the claimed substrates, such portability is also held to be obvious absent new or unexpected results (See *In re Lindberg*, 194 F.2d. 732, 93 USPQ (CCPA 1952) & MPEP 2144.04 (V)).

Therefore, the invention as claimed is obvious over the cited reference.

Conclusion

No claims are allowed.

The rejection of claims 56-61, 64-68, 84-93, and 96-99 under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (US 2003/0027126 A1, published February 6, 2003) has not been made in the instant Office Action based on the finding that the parent applications of Walt et al., namely U.S. Application 09/450,829 (filed November 29, 1999) and U.S. Application 08/818,199 (filed on March 14, 1997), did not support the new pyrophosphate sequencing reagents comprised on an immobilized bead (*i.e.*, limitation of the instant claims), rendering the Walt et al. reference not a prior art reference.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (703) 308-9348. The Examiner can normally be reached from 8:30 a.m. to 7:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (703)-308-3905. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (703) 308-1119. Papers related to this

Art Unit: 1637

application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (703) 872-9306. For Unofficial documents, faxes can be sent directly to the Examiner at (703) 746-3172. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Young J. Kim

10/31/03


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